FINAL REPORT - Grant NsG 75 - 60

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New funds for grant NsG 75 - 60 were not appropriated from July 1, 1966 and work was supported by the unexpended funds of that date.

The original proposal, made in 1960, was to study the magnitude and degree of protection afforded by a combination of deep hypothermia and immersion in a fluid against accelerative stress. The objective was attained[1, 2] using three small mammals; the mouse, the rat and hamster. The mouse being an obligate nasal breather, the small calibre of the nasal passage posed a major obstacle, since it was almost always blocked during centrifugation by mucus and blood. This was circumvented by substituting the rat as the test animal. Excellent results were achieved with permanent protection against 5 minutes of 2,300 G. Although revival presented no difficulties, beyond this time the animals invariably died. The major lesion was a characteristic hemorrhagic gastroenteropathy. This lesion was described and study indicated it was, in good part, due to proteolytic digestion during cold suspended animation. A paper was presented to the American Association of Pathologists and Bacteriologists meeting in Montreal in 1962.[3] The theme emphasized the probability that the enteropathy of prolonged deep hypothermia and irreversible shock were identical. This presentation inspired Buonous in Montreal to launch a series of investigations of canine irreversible hemorrhagic shock which, in all details, corroborated our work.

Since the enteric lesion appeared to be an obvious obstacle to the successful prolongation of deep hypothermia, means of preventing the lesion were sought.[4] Utilizing soy-bean-trypsin inhibitor we

demonstrated that although prevention of digestion could be achieved, shedding of the gut epithelium and its mucus coat proceeded apace. Obviously this loss would be a catastrophe inevitably leading to destruction of the underlying lamina propria or, and equally catastrophic, a loss of selective absorption from the gut lumen. After considerable work it was learned that the epithelial shedding was an osmotic lysis (osmolysis). The mechanism proposed was the continued passive diffusion of hydrated Na ions into the cells in the absence of active ionic pumping normally powered by energy now inhibited by the cold. This culminated in the bursting of the epithelial cells and eventual digestion of the defenseless lamina propria.

By analogy and using isolated data in the literature it was suggested that the same phenomenon materialized during profound shock through hypoxic inhibition of oxidative phosphorylation whence the ionic pumps are powered.

The latest phase of this work has turned to the kidney. Since the function of both gut and kidney are strikingly similar and many of the mechanisms are common to both, it was reasoned that the kidney, like the gut, should show the characteristic lesion of shock, lower nephron nephrosis. This prediction has most recently been confirmed.

In summarizing this aspect of our work, it may be said that the limiting factor in the prolongation of deep hypothermia is the profound disturbance about the cell membrane of the steady state equilibrium of those asymmetrically distributed substances to which the membrane is permeable.

An unexpected dividend arising from this work is the recognition that in acute severe heart failure the use of oral digitalis may constitute a threat to the patient's life.[5] Well known to pharmacologists and physiologists but not to physicians is the fact that digitalis preparations are excellent inhibitors of the Na^+ and K^+ pumps via an effect upon the specific ATPase. The addition of an electrolyte transport inhibitor such as digitalis to the gut of one who is already suffering tissue hypoxia may account for the high incidence of hemorrhagic enteropathy in cardiac failure. The parenteral administration of digitalis in acute failure may prevent the fatal lesion.

Fine et al have suggested that irreversible shock is brought about through the absorption from damaged gut of Shwartzman potent toxins of bacterial origin which block the reticuloendothelial system thus sensitizing the subject to other shock inducing stimuli. Since one of the ingredients of the gut mucin is a negatively charged sulfated polysaccharide and such polyelectrolytes are known to enhance the Shwartzman phenomenon, an investigation[6] of a series of such mucopolysaccharides and their anionic derivatives was undertaken. It was learned that nonionic polysaccharides had no effect upon the R-E system but that the negatively charged polymers did. The effect was directly related to the molecular size. The larger the molecule the more effective. Thus it is now possible to say that if mucus or its water soluble components are absorbed from the intestine during shock what may have been reversible shock may well become irreversible, without the agency of bacterial products.

Equilibrium disturbances[7] were manifested immediately after revival of centrifuged animals. This was investigated in the hamster and it was shown that the lesion was identical to a hemilabyrinthectomy. The side to be involved could be selected by proper positioning of the hamster. Despite the magnitude of the symptoms and signs the lesion was completely reversible within two to three weeks. It was suggested that the hypothermia by increasing the viscosity of the gelatinous membrane bearing the otoconia minimized the migration of the otoliths in the centrifugal field. In this manner hypothermia amplified a physiologic protective mechanism.

Because of a continuing interest in cardiac pathology[8, 9] a study was undertaken of large mammalian hearts with particular reference to the presence and function of a fibroelastic internal membrane.[10] It was concluded that the normal muscle fibers of a small mammal such as the rat differed very little in size from those of a large (72 ton) whale despite a 10^5 difference in the weights of the hearts. In short, nature increases the power of the heart by adding additional units of essentially the same size. A device to reduce the strain on the heart is incorporated in very large normal (and some large abnormal hearts) namely an internal fibroelastic membrane which reduces the diastolic tension to be borne by the muscle.

A further study[11] concerns the contraction rates of isolated heart muscle fibers from newborn animals with widely varying spontaneous cardiac rates. The results have not yet been submitted for publication, however, they indicate that the normal cardiac contraction rate is a reflection of the work load and that the relationship is direct.

The preceding two studies are directly pertinent to an understanding of the chronic effects of reduced or null gravity upon the mammalian heart.

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